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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/396,710	09/15/1999	AVI J. ASHKENAZI	P1101P2	7837

7590 03/17/2003

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 03/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/396,710	Applicant(s) ASHKENAZI ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 1999 and 02 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 10-13* is/are rejected.

7)☐ Claim(s) *6-9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,6,11,13,15+16
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The application is no longer suspended.

Information Disclosure Statement

The IDS submitted Jan. 27, 2000 has been considered to the extent possible. Several of the references said to be submitted in parent or sibling applications were either not present or not considered: 90,103, 106, 115, 116, 122, 126,167, 172, 179, 198, 204,209 and 277. Reference # 51 (Kabat) of the IDS submitted March 4, 2003, was missing and could not considered.

Claim Rejections - 35 USC § 112

Claims 1-5 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing apoptosis in mammalian cells expressing Apo-2 by using an Apo-2 agonist antibody, wherein the antibody binds to an Apo-2 polypeptide consisting of the contiguous amino acid residues 1 to 411 of SEQ ID NO:1, does not reasonably provide enablement for use of an antibody binding to a sequence other than that set forth above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of inducing apoptosis with an agonistic antibody that binds Apo-2. The specification teaches antibodies made to the extracellular fragment of amino acids 1-184 of SEQ ID NO:1 (p.72, lines 17-19) of Apo-2, the receptor for Apo-2L. Agonist antibodies were isolated (Example 10, p. 74). No other antibodies to an Apo-2 beside the Apo-2 polypeptide of SEQ ID NO:1 had been identified such that antibodies made to a different sequence would be expected to bind the disclosed receptor and produce the required agonistic function.

The prior art does not teach an Apo-2 polypeptide. It does teach related polypeptides Apo-3/DR3 (Marsters et al., 1996, #195 cited by Applicants) and DR4 (Pan et al., 1997, #230 cited by Applicants). Also taught is an antibody to Apo-3 (Marsters et al., *ibid.*, see p. 1675, 5th paragraph), but that antibody would not be expected to bind Apo-2 as the disclosed sequence of Apo-2 and Apo-3 share only about 24% identity overall and 34% identity in the death domain.

Therefore, the prior art does not teach an antibody that would reasonably be expected to bind Apo-2. It is acknowledged that the skill in the art is high as it relates to the discovery of TNF receptor family proteins, of which Apo-2 is a member, but not as it relates to predicting sequences of the receptor proteins or, as a result, the necessary structure of an antibody that would bind an unknown member of the receptor family. It was known at the time the invention was made that the ligand for Apo-2 (called Apo-2L or TRIAL) is involved in causing apoptotic cell death (p. 2, lines 26-33 or the specification).

The breadth of the claims as they relate to "Apo-2", recited only by name, is very broad since the specification includes "variants" in the definition. The term Apo-2 as defined in the specification includes naturally occurring and variant polypeptides (p. 12, lines 15-18 and p. 13, lines 13-26) . According to the specification (p. 12, lines 8-18), a variant must be a biologically active Apo-2 and have at least 80% amino acid sequence identity with SEQ ID NO:1. "Biologically active" is broadly defined as the ability to modulate (stimulate or inhibit) apoptosis (page 17, lines 29-35). Because of the low sequence identity of SEQ ID NO:1 to known related receptors, it is not predictable what other sequences an Apo-2 polypeptide could have while still being "biologically active" and distinguishable from other receptors of the TNF receptor family. The only Apo-2 polypeptide disclosed has SEQ ID NO:1, and no other naturally occurring or variant receptors are disclosed.

For these reasons which include the unpredictability and lack of teaching of making an antibody which bound to a polypeptide not identical to SEQ ID NO:1 yet still induced apoptosis, and the breadth of the claims due to the variation in Apo-2 sequence permitted, it would require undue experimentation to practice the claimed invention as it is currently claimed.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 6,072,047 is cited in IDS paper #6 and teaches an Apo-2 polypeptide called TRAIL-R of SEQ ID NO:2. This patent receives benefit of priority to 08/829,536, filed March 28, 1997, for the full-length receptor polypeptide, which is identical to SEQ ID NO:1 of the instant application with the exception that TRAIL-R has a 39 amino acid insert beginning at either position 182 or 185 of SEQ ID NO:2 of the patent, which insert occurs after amino acid

181 or 184, respectively, of SEQ ID NO:1 of the instant application. However, the concept of **agonistic** antibodies does not appear until priority application 08/869,852, filed June 4, 1997, and the artisan of ordinary skill would have no motivation to practice the claimed method with an agonistic antibody based on the disclosure of the '536 application. This patent is, therefore, disqualified as prior art. As an aside, it is noted that the concept of antagonistic antibodies is taught in 08/869,852.

US Patent 6,342,369 shares a common inventor with the instant application. The claimed subject matter is different from that being claimed in the instant application This patent is not available as prior art, the earliest possible effective filing date being later than the effective filing date of the instant application. It is also noted that amino acids 32 and 410 are different between SEQ ID NO:2 of the patent and SEQ ID NO:1 of the instant application.

In IDS paper#15, US Patent 6,313,269 is made of record. This patent is not available as prior art because it does not receive priority before August 22, 1997, for while the full sequence of Apo-2 is disclosed in 08/853,684, filed May, 9, 1997, there is no contemplation of agonistic antibodies and the artisan of ordinary skill would have not motivation to practice the claimed method based on the disclosure of the'684 application with an agonistic antibody. Additionally, its provisional application 60/041,230 (Mar. 14, 1997) only discloses amino acids 109 to 411 of SEQ ID NO:1 of the instant application, which is not sufficient basis for anticipation or obviousness of the claimed invention. Additionally, it is noted that amino acid 106 is different between SEQ ID NO:2 of the patent 6,313,269 and SEQ ID NO:1 the instant application.

Conclusion

Claim 6-9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

March 12, 2003